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Hormone Resistance Caused by Mutations in G Proteins and G Protein-coupled Receptors

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ABSTRACT

G proteins couple receptors for many hormones to effectors that regulate second messenger metabolism. Several endocrine disorders have been shown to be caused by either loss or gain of function mutations in G proteins or G protein-coupled receptors. Pseudohypoparathyroidism (PHP), the first described example of a hormone resistance disorder, is characterized by renal resistance to parathyroid hormone (PTH) proximal to generation of the second messenger, cAMP. In PHP Ia there is more generalized hormone resistance (PTH, TSH, gonadotropins) and associated abnormal physical features, Albright hereditary osteodystrophy (AHO). Subjects with PHP Ib are normal in appearance and resistant exclusively to PTH. Germline loss of function mutations have been identified in the G_S-α gene in PHP Ia, and recent evidence suggests that the G_S-α gene is paternally imprinted in a tissue-specific manner. In PHP Ib, several studies have excluded PTH receptor gene mutations, and the molecular basis has not yet been defined.

KEY WORDS

receptors, G proteins, mutations, pseudohypoparathyroidism, McCune-Albright syndrome

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INTRODUCTION

Heterotrimeric G proteins couple hundreds of receptors for hormones, growth factors, neurotransmitters, odorants and other extracellular "first messengers" to effectors such as adenylyl cyclase, phospholipase C β, and various ion channels[1-3]. In the past few years, an increasing number of human diseases, particularly endocrine diseases, have been shown to be caused by mutations in either G proteins or G protein-coupled receptors (GPCR)[4,5]. In this review, I give a very brief overview of G protein-coupled signal transduction, provide a general background on disorders caused by mutations in G proteins and GPCR, and then focus on one well-studied example of hormone resistance, pseudohypoparathyroidism (PHP).

G PROTEIN-COUPLED SIGNAL TRANSDUCTION

The literature on the structure and function of proteins involved in G protein-coupled signal transduction is vast and continually expanding. Given the limited scope of the present review, I cite only some recent reviews[1-3] from which the interested reader can obtain greater detail than from the following overview. G protein-coupled signal transduction minimally involves three components: GPCR, the G proteins themselves, and G protein-regulated effectors. Recently, a family of proteins, the RGS family, that activates G protein GTPase activity, has been identified as a fourth component of this signal transduction pathway[6], and yet additional components may remain to be discovered.

GPCR comprise a huge superfamily, all members of which share certain common features: a structure characterized by seven membrane-spanning α helices, and a function consisting of agonist binding leading to interaction with and activation of a G protein[7]. G proteins are heterotrimers composed of

three subunits, α, β, and γ, each the product of separate genes. The latter two subunits form a tightly, but noncovalently associated functional unit, the β/γ dimer. In the basal state, the α subunit tightly binds GDP and is associated with the β/γ dimer. GPCR activation of the G protein leads to release of tightly bound GDP, replaced by binding of GTP which is present in the cell at ten-fold higher concentration than GDP. GTP binding causes a significant change in conformation of the α subunit such that it dissociates from GPCR and β/γ, and binds instead to specific effector proteins. The effector proteins include enzymes of second messenger metabolism and ion channels. They are regulated (activation or inhibition) by α subunits, the β/γ dimer and sometimes by both. The GTPase activity of the α subunit, accelerated by the RGS protein (see above), converts bound GTP to GDP and terminates effector binding, as well as allowing the β/γ dimer to reassociate. This GTPase cycle (see Figure 1) is the essential feature of G protein-coupled signal transduction, the conversion of an extracellular signal into a change in intracellular second messenger and/or ion concentration, thereby altering cellular function acutely and chronically.

The great diversity in GPCR is not equalled for the G proteins and effectors, but there are at least sixteen different α subunit genes, five β subunit genes and over a dozen γ subunit genes. The list of G protein-regulated effectors is growing but may be in the range of 10-20. Diversity in the components of G protein-coupled signal transduction raises the question of specificity in coupling of the various components. In part, specificity is achieved through differences in the range of expression of various components. Thus many receptors and certain G proteins are quite restricted in distribution. Others are expressed ubiquitously, and a given cell may coexpress multiple GPCR, G proteins and effectors. Coupling is nonetheless relatively specific, largely because of differences in sequence and structure of the respective protein interaction domains. Such specificity is important in considering the clinical consequences of a germline mutation in a given G protein α subunit or GPCR. In general, the more limited the range of expression, the more localized the phenotypic consequences of mutation, and vice versa.

MUTATIONS IN G PROTEINS AND G PROTEIN-COUPLED RECEPTORS AND HUMAN DISEASE: GENERAL OVERVIEW

Mutations in G proteins and GPCR may be loss- or gain-of-function mutations (see Figure 1). Loss-of-function mutations may involve almost any part of the protein, e.g. by truncating the protein or otherwise interfering with expression and membrane targeting of a normally folded protein. Even when a mutation permits correct general folding and targeting, subtle missense mutations may impair key functions of the α subunit such as receptor or β/γ dimer interaction, or of the GPCR such as agonist binding or G protein interaction. Gain-of-function mutations tend to be more limited in scope. For GPCR, such mutations are thought to cause an agonist-independent conformational change that leads to constitutive activation. For G protein α subunits, missense mutation of two key residues (arginine 201 and glutamine 227 in Gs-α) leads to constitutive activation by inhibiting the "turnoff" GTPase activity.

Loss-of-function mutations involving GPCR and G proteins that mediate hormone action in general cause hormone resistance, whereas gain-of-function mutations lead to apparent endocrine hyperfunction. Moreover, loss-of-function mutations are in general recessive and must be homozygous (or hemizygous in males with X-linked nephrogenic diabetes insipidus) before causing disease, while gain-of-function mutations are dominant; and therefore heterozygous mutation is sufficient to cause disease. The calcium-sensing receptor which when activated by extracellular ionized calcium inhibits parathyroid hormone (PTH) secretion and promotes renal calcium excretion[8] is an exception to these rules in that even heterozygous loss-of-function mutation leads to "resistance" to calcium. The resulting disorder, familial hypocalciuric hypercalcemia, mimics parathyroid gland hyperfunction with PTH hypersecretion. Indeed, homozygous mutation leads to the more severe phenotype, neonatal severe primary hyperparathyroidism. In contrast, gain-of-function mutation of the calcium-sensing receptor leads to activation at inappropriately low serum ionized calcium, and the resultant inhibition of PTH secretion and promotion of renal calcium excretion

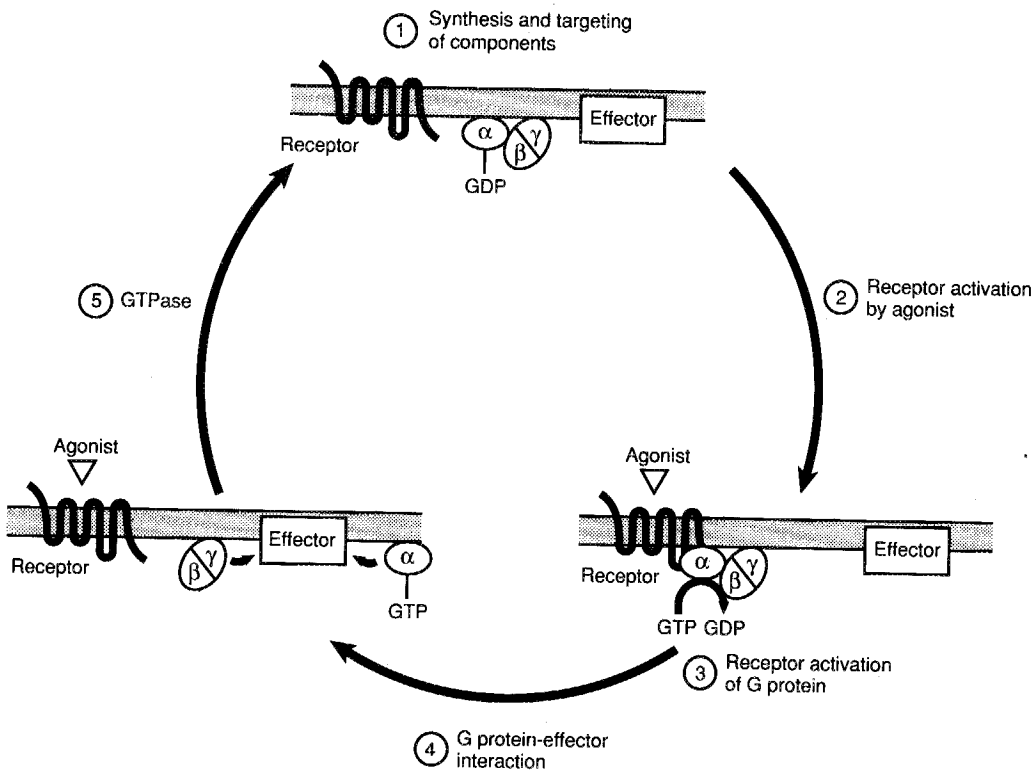

Fig. 1: The G protein GTPase cycle. Potential sites for disease-causing abnormalities are numbered. In each panel, the stippled region denotes the plasma membrane with extracellular above and intracellular below. In the basal state, the G protein is a heterotrimer with GDP tightly bound to the α subunit. The agonist-activated receptor catalyzes release of tightly bound GDP which permits GTP to bind. The GTP-bound α subunit dissociates from the βγ dimer. Arrows between GTP-bound α subunit and effector and between βγ dimer and effector indicate regulation of effector activity by the respective subunits. Under physiologic conditions, effector regulation by G protein subunits is transient and is terminated by the GTPase activity of the α subunit. The latter converts bound GTP to GDP, thus returning the α subunit to its inactivated state with high affinity for the βγ dimer which reassociates to again form the heterotrimer.

leads to hypoparathyroidism with paradoxical hypercalciuria.

Many hormone resistance disorders have now been identified that are caused by loss-of-function mutations in GPCR (see Table 1), including resistance to vasopressin, TSH, TRH, GHRH, ACTH, and LH[5]. Gain-of-function mutations in the LH, TSH, and PTH receptors have been identified as the cause of diseases mimicking hypersecretion of these hormones[5]. Gain-of-function mutations of the Gs-α gene that encodes the protein responsible for coupling many receptors to adenylyl cyclase have been identified in McCune-Albright syndrome[4,5] and in some isolated somatotroph and thyroid tumors[4,5]. Loss-of-function mutations in the Gs-α gene in a form of PHP will be discussed in detail below.

PSEUDOHYPOPARATHYROIDISM

As originally proposed by Albright *et al.*[9], defective target organ response to PTH should lead to the same consequences, hypocalcemia and hyperphosphatemia, as deficiency of the hormone. Renal resistance to PTH would cause loss of the phosphaturic response and lead to hyperphosphatemia. The latter and/or primary resistance to PTH would lead to diminished formation of 1,25-dihydroxyvitamin D. 1,25-Dihydroxyvitamin D deficiency, by reducing gastrointestinal absorption of calcium, also contributes to hypocalcemia. Albright *et al.* described three patients with PTH resistance and termed the disorder pseudohypoparathyroidism (PHP)[9]. He also noted certain abnormal physical

TABLE 1

Hormone resistance diseases caused by GPCR loss of function mutations

Receptor	Disease	Inheritance
V2 vasopressin	nephrogenic diabetes insipidus	X-linked
ACTH	familial ACTH resistance	aut. rec.
LH	male pseudohermaphroditism	aut. rec.
TSH	familial hypothyroidism	aut. rec.
CaR	familial hypocalciuric hypercalcemia/	aut. dom.
	neonatal severe primary hyperparathyroidism	aut. rec.
Endothelin B	Hirschsprung disease	aut. rec.
FSH	hypergonadotropic ovarian failure	aut. rec.
TRH	central hypothyroidism	aut. rec.
GHRH	GH deficiency	aut. rec.
GNRH	hypogonadotropic hypogonadism	aut. rec.
PTH	Blomstrand chondrodysplasia	aut. rec.

features in his patients with PHP, including short stature, obesity, round face, short neck and shortened metacarpals and metatarsals. These phenotypic features have been termed collectively Albright hereditary osteodystrophy (AHO). Subsequently, other patients were described who showed PTH resistance but lacked features of AHO. Both groups, however, were characterized by deficient excretion of urinary cAMP, a measure of renal response to PTH, after PTH infusion[10]. The site of the defect in both forms of the disorder was therefore proximal to cAMP generation, presumptively within the PTH receptor-Gs-adenylyl cylase components of the signal transduction pathway.

In most patients with PHP and AHO, heterozygous loss-of-function mutations in the Gs-α gene have been identified[11]. This form of the disorder has been termed PHP Ia. In many cases the mutations result in abnormal RNA processing and lack of expression of the mutant allele (i.e. base substitution at a splice junction site, coding frameshift mutations, premature stop codons, and large deletions[12-24] [and L.S. Weinstein, unpublished data]). One specific 4 base pair (bp) deletion within exon 7 of *GNAS1* has been identified in affected members from multiple unrelated PHP Ia kindreds[13,19-22]. This deletion hotspot coincides with a consensus sequence for arrest of DNA polymerase α and likely results from arrest of polymerization and slipped strand mispairing during DNA replication[20].

Missense mutations in *GNAS1* have also been identified. In some cases the encoded amino acid substitution (L99P and R165C[14]; S250R[25]) appears to globally alter tertiary structure or intracellular trafficking of the Gs-α protein, since in each case the level of Gs-α mRNA is normal but the level of membrane Gs-α protein is decreased. In one kindred, a mutation at the translational start site codon results in the expression of an abnormally large form of Gs-α protein which is presumed to be nonfunctional[26]. One missense mutation (R385H) identified in the carboxy-terminal region results in a specific defect in receptor coupling[27]. Another missense mutation (A366S) within a region encoding a portion of the highly conserved guanine nucleotide binding site was identified in two unrelated males who presented with Albright osteodystrophy and PTH resistance in association with gonadotropin-

independent precocious puberty[28]. This mutation was shown to decrease the protein's affinity for GDP. At internal body temperature (37°C) Gs-α unbound to guanine nucleotide is unstable, leading to decreased expression of Gs-α protein and the clinical expression of AHO and hormone resistance. At slightly lower temperatures (the ambient temperature of the testes) this mutation leads to Gs activation, increased intracellular cAMP and gonadotropin-independent precocious puberty (interestingly mimicking what is seen with other activating mutations of Gs-α in McCune-Albright syndrome or of the LH receptor in familial male precocious puberty), since GDP release is normally the rate-limiting step in G protein activation. A mutation (R231H) within a region of Gs-α that undergoes a major conformational shift upon receptor-activation (switch 2 region) has been shown to cause a specific defect in activation by receptor or the transition state analog aluminum fluoride[29,30]. A mutation (R258W) within the switch 3 region has been demonstrated to cause an increased rate of GDP release[31].

Impaired adenylyl cyclase stimulation due to Gs deficiency leads to resistance not only to PTH in patients with PHP Ia, but also to certain other hormones whose receptors are coupled to Gs such as TSH and gonadotropins. Yet resistance to other hormones with Gs-coupled receptors such as vasopressin and ACTH is not clinically apparent in PHP Ia. Furthermore, in families with PHP Ia, some members show subtle features of AHO but no evidence of resistance to PTH, TSH or other hormones. Such individuals are said to have pseudoPHP (PPHP) and have been found to show the identical Gs-α gene mutations as their relatives with PHP. Recent clinical genetic studies[18,22,32], as well as studies in mice with a targeted mutation of the Gs-α gene[33], suggest that imprinting of the Gs-α gene is likely the basis for the variable presentation of patients with Albright osteodystrophy (PHP Ia vs. PPHP), although this has not been formally proven [34,35]. Paternal imprinting of the gene would mean that only the allele inherited from the mother is normally expressed. Thus if the mutant Gs-α gene is inherited from the father, the result would be PPHP, but if the mother is the source of the mutant gene, there would be loss of the normally expressed allele, severe Gs deficiency, and the phenotypic result would be PHP Ia. Recent data in a mouse model of Gs deficiency[33] suggest that tissue-specific imprinting of the Gs-α gene is the cause of the differences in hormone resistance seen clinically in PHP Ia.

In patients with PHP without AHO, resistance is generally limited to the renal response to PTH and is termed PHP Ib. The PTH receptor was an obvious candidate gene for this disorder with loss-of-function mutation leading to a PTH-specific form of hormone resistance by analogy with other hormone resistance disorders caused by loss-of-function mutations in their cognate GPCR, e.g. nephrogenic diabetes insipidus. Molecular genetic studies, however, have failed to identify mutations in the PTH receptor gene in patients with PHP Ib[36,37]. Given the lethal phenotype of homozygous disruption of the PTH receptor gene in mice and in the human disease, Blomstrand chondrodysplasia[38], it appears unlikely that PHP Ib could be caused by homozygous loss-of-function mutation of the PTH receptor, but more subtle abnormalities have yet to be completely excluded[36]. An analysis of the promoter region of the PTH receptor gene revealed a general as well as a renal-specific promoter, but no specific defect in the promoter regions could be identified in seven PHP Ib patients[39]. A defect in a renal-specific signal transduction component proximal to cAMP generation in response to PTH remains the most likely cause of PHP Ib but the identity of this component is at present unknown.

CONCLUSIONS

The study of humans with PTH resistance illustrates well how basic understanding of G protein-coupled signal transduction has helped elucidate the pathogenesis of hormone resistance, and at the same time how detailed analysis of differing forms of PTH resistance has increased our understanding of such basic issues as G protein structure, function and gene regulation. Further studies of both humans with PTH resistance, as well as mouse models such as the Gs-α gene knockout[33], will help to clarify the complexities of Gs-α gene regulation including imprinting, and the basis of renal-specific resistance to PTH in PHP Ib. With further insights into the pathogenesis of these and other human diseases involving mutations in G

proteins and GPCR[5] will come new opportunities for diagnosis and treatment.

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